REMARKS

Claims 1, 3-19, and 21-36 are pending in the present application. Claims 11 and 29 have been canceled. Claims 1 and 19 have been amended, and new claims 37-39 have been added. Support for new claim 37 is found in the specification at page 12, lines 16-22. Support for new claim 38 is found in the specification at page 12, line 16 to page 13, line 4. Support for new claim 39 is found in the specification at page 12, line 16 to page 13, line 1. Applicant requests reconsideration and allowance of claims 1, 3-10, 12-19, 21-28, and 30-39 in light of the amendments to the claims and the following remarks.

Rejections of Claims under 35 U.S.C. §103(a)

In the previous final Office Action in the pending application, claims 1, 3-19, and 21-36 were rejected under 35 U.S.C. §103(a) as being unpatentable over Lozada in view of Qi et al (WO 97/31921). The Office Action rejected the Applicant's argument that there is no motivation in the prior art to combine the cited reference to arrive at the invention as claimed. The rejection is respectfully traversed.

Claims 1 and 19 are amended to recite that the composition used in the methods of the invention consists of a pharmaceutically acceptable carrier, one of a limited number of immunosuppressive agents, and optionally a non-steroidal anti-inflammatory agent. Nothing in the cited prior art, alone or in combination, teaches or suggests a method for treating an oral autoimmune disease by topical application of the composition recited in claims 1 or 19. Accordingly, withdrawal of the rejections of pending claims 1, 3-10, 12-19, 21-28, and 30-36 under 35 U.S.C. §103(a) is respectfully requested.

The Final Office Action stated "One of ordinary skill in the art would have been motivated to employ the immunsuppressive azathioprine, alone or in combination with an anti-inflammatory agent..." (Final Office Action, page 5, lines 6-10). Applicant respectfully disagrees with this conclusion. Nothing in the cited prior art would have led one of ordinary skill in the art to believe that an autoimmune disease of the mouth could be treated by topically

applying azathioprine, in the absence of prednisone (Lozada) or a triptolide analog (Qi et al.). Moreover, both references cited in the Office Action teach the use of systemic azathioprine in combination with the immunosuppressive compound. Neither reference expressly teaches the topical application of azathioprine to treat an oral autoimmune disease, in the absence of the immunosuppressive compound taught therein.

It is known in the art that systemically administered azathioprine is undesirable because of its potentially severe side effects, which include blood abnormalities (especially leukopenia), low WBC count, and increased cancer risk (Lozada, page 259, col. 1). In addition, systemically administered azathioprine is known to induce myelosuppression, hypersensitivity, mild gastrointestinal reactions, and adverse drug interactions, and the intravenous preparation of azathioprine is an extreme irritant (see A. Anstey and J.T. Lear, *Azathioprine: Clinical Pharmacology and Current Indications in Autoimmune Disorders*, BioDrugs 1998, 9(1):33-47, at pages 36, 37-39; A. Winkelstein, *The Effects of Azathioprine and 6-MP on Immunity*, J. Immunopharmacology 1979 1(4):429-454, pages 445-446). Thus, corticosteroids are overwhelmingly preferred by those of skill in the art for the treatment of oral autoimmune diseases (Woo, S.-B. et al., *Crit. Rev. Oral Biol. Med.*, 1997 8(2):201-216, at page 209, col. 2, first full paragraph). All references cited above are already of record in this application.

To achieve the instant invention as presently claimed, the teachings of Lozada et al. would have to be drastically modified. One would first have to be motivated to remove the prednisone component, and then reformulate the azathioprine from a systemic formulation (i.e., in the form of a tablet) into a format suitable for topical administration. Removal of the prednisone would mean loss of what the cited reference itself calls one of the most effective drugs for treatment of chronic inflammatory mucocutaneous diseases (Lozada, page 257, first column). Supplying azathioprine in a format suitable for topical administration is further undesirable to one of skill in the art, because azathioprine is known to be an extreme irritant. Nothing in the references cited in the Office Action provides the high level of motivation required to modify these teachings so drastically. In fact, Lozada and the rest of the prior art teaches the opposite. Lozada teaches that a beneficial synergistic effect is obtained when predisone is combined with azathioprine, and that treatment of acute stage MMP with azathioprine alone is inferior to combined treatment with prednisone (page 259, second column).

Moreover, Lozada and the prior art illustrate the significant risks and adverse side-effects that accompany the use of systemically administered azathioprine, which would discourage one of skill in the art from making such modifications.

Nothing in Qi et al. provides motivation to modify the references either so as to achieve the presently claimed invention. Qi et al. is concerned with the use of triptolide analogs in the treatment of autoimmune disorders. The triptolide analogs of Qi et al. are steroidal derivatives. Qi et al. mentions azathioprine only as a drug optionally coadministered with the triptolide analogs (page 19, lines 3-12 – "In the potentiated immunosuppressant therapy method of the invention, a triptolide analog of Formula 1 above *may be administered with an immunosuppressant drug* together in the same formulation, or separately in separate formulations...The immunosuppressive drug *which is administered with the triptolide analog* is preferably one of the following:...(c) azathioprine,..."). Nothing in Qi et al. provides any motivation at all for one of skill in the art to modify the teachings of Qi et al. by administering azathioprine alone, in the absence of the triptolide analogs taught by the specification. Even less does Qi et al. provide any motivation to employ a topically useful formulation of azathioprine without the triptolide analogs disclosed therein, which form the basis for the teachings of this reference. Consequently, Qi et al. provides even less of a teaching for the use of azathioprine by itself in autoimmune diseases than Lozada.

The Office Action does not dispute the Applicant's contention that Lozada teaches a synergistic interaction between the anti-inflammatory agent and the azathioprine in the compositions disclosed therein. Rather, the Office Action stated that one cannot conclude that the immunosuppressive activities of azathioprine will be diminished if the anti-inflammatory agent is removed (Office Action, page 5, second paragraph). Applicant respectfully disagrees with this conclusion. If the interaction with prednisone is synergistic, then by definition one must conclude that the immunosuppressive activities of azathioprine will be diminished if the anti-inflammatory agent is removed. Webster's Third New International Dictionary defines "synergy" as "cooperative action of discrete agencies (such as drugs or muscles) such that the total effect is greater than the sum of the two or more effects taken independently". Applicant does not argue that Lozada teaches azathioprine has no activity when used alone. Rather, Applicant submits that the teaching by Lozada of synergistic interactions between azathioprine

and predisone would lead one of ordinary skill in the art away from the use of either prednisone or azathioprine alone to treat vesiculoerosive oral diseases.

The Office Action points out (page 6, first paragraph) that while Applicant referred to some prior art references in the previous Response, there is no showing in the instant specification of diminished side effects of azathioprine. Applicant respectfully submits that the reference in the previous Response to that prior art was made in the context of demonstrating the known adverse side effects of systemically administered azathioprine. The Applicant did not intend to establish diminished side effects of topically administered azathioprine; only to establish that one of skill in the art would not have been motivated to modify the teachings of Lozada to remove the anti-inflammatory component prednisone.

Nothing in either Lozada or Qi et al. provides sufficient motivation to make the drastic modifications to the teachings of those references that would be necessary to arrive at the invention as presently claimed. Applicant respectfully submits that the invention as claimed in claims 1, 3-10, 12-19, 21-28, and 30-39 is patentable. Accordingly, Applicant respectfully requests reconsideration and allowance of claims 1, 3-10, 12-19, 21-28, and 30-39.

Applicant hereby requests a three-month extension of time under 37 CFR 1.136 to respond to the pending Final Office Action in this application. No additional fee is believed to be required for entry of this Preliminary Amendment. However, should any such fee be required, the Commissioner is authorized and requested to charge any such amounts, including any additional extension of time fees, to the Deposit Account of the undersigned attorneys, which is: **Deposit Account No. 12-2475.**

PATENT
Attorney Docket No. 247/164

Should the Examiner have any further comments or questions, or believe that certain actions would expedite the issuance of the present application, the Examiner is invited to telephone the Applicant's representative at the number listed below.

Respectfully submitted,

LYON & LYON LLP

Dated: March 25, 2002

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PATENT
Attorney Docket N . 247/164

VERSION WITH MARKING TO SHOW CHANGES MADE

1. (Amended) A method for treating an autoimmune disease of the mouth, comprising topically contacting the mouth of a patient in need of such treatment with a formulation consisting [essentially of an effective amount of] of a pharmaceutically acceptable carrier a member selected from the group consisting of azathioprine, 6-mercaptopurine, 6-thioguanine nucleotide, a pharmaceutically acceptable salt of azathioprine, a pharmaceutically acceptable salt of 6-mercaptpurine, and a pharmaceutically acceptable salt of 6-thioguanine nucleotide, and optionally a non-steroidal anti-inflammatory agent. [or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.]

19. (Amended) A method for preventing an autoimmune disease of the mouth, comprising topically contacting the mouth of a patient in need of such treatment with a formulation consisting [essentially of an effective amount of] of a pharmaceutically acceptable carrier a member selected from the group consisting of azathioprine, 6-mercaptopurine, 6-thioguanine nucleotide, a pharmaceutically acceptable salt of azathioprine, a pharmaceutically acceptable salt of 6-mercaptpurine, and a pharmaceutically acceptable salt of 6-thioguanine nucleotide, and optionally a non-steroidal anti-inflammatory agent. [or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.]

Claims 11 and 29 have been canceled.

Claims 37-39 are new.

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Serial No.:	09/433,418
For:	TOPICAL AZATHIOPRINE FOR THE TREATMENT OF ORAL AUTOIMMUNE DISEASES
Filed:	November 4, 1999
Attorney(s):	Charles M. Doyle, Esq.
Docket No.:	247/164
Date of Deposit:	March 25, 2002
Express Mail:	EV 056390664 US
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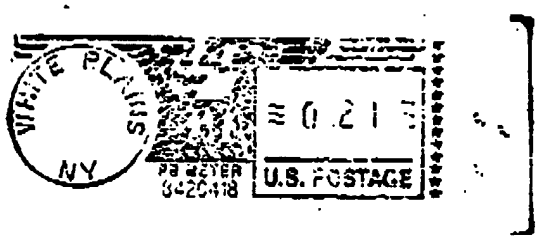

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